Exhibit 4

Chronology of Events on CAMPTOSAR® (Irinotecan Hydrochloride Trihydrate) IND 35,229; NDA 20-571

DATE	EVENT
August 3, 1990	G.H. Besselar Associates submitted IND for CPT-11 on behalf of Kabushiki Kaisha Yakult Honsha.
August 6, 1990	Letter from FDA acknowledging the August 6, 1990 submission and assigning IND number 35,229.
August 15, 1990	G. H. Besselar letter submitting to FDA an additional copy of the IND.
October 22, 1990	G.H. Besselar submits Response to FDA Request for Additional Protocol Amendment: Change in Protocol New Investigator.
March 4, 1991	G.H. Besselar submits Protocol Amendment: Change in Protocol.
March 6, 1991	G.H. Besselar submits Protocol Amendment: New Protocol.
March 18, 1991	G.H. Besselar submits Other: Additional Secondary Investigators.
April 9, 1991	G.H. Besselar submits Protocol Amendment: Change in Protocol.
August 1, 1991	G.H. Besselar submits Change in Protocol (GHBA-393).
October 3, 1991	G.H. Besselar submits Protocol Amendment: New Investigator.
October 9, 1991	G.H. Besselar submits Annual Report.
October 16, 1991	G.H. Besselar submits Protocol Amendment.
January 14, 1992	G.H. Besselar submits Protocol Amendment: Change in Protocol.
October 1, 1992	G.H. Besselar submits Annual Report.

DATE	EVENT
November 4, 1992	G.H. Besselar submits Response to FDA Request for Information.
November 30, 1992	G.H. Besselar submits errors correct in the 1992 Annual Report.
December 8, 1992	Theradex submits transfer of representative agent from G.H. Besselar to Theradex.
January 11, 1993	Theradex submits Request for Compassionate Use.
January 28, 1993	Theradex submits Request for Compassionate Use.
January 28, 1993	Theradex submits Request for Compassionate Use.
February 1, 1993	Theradex submits Prorovol: Cervical Cancer Phase II, M.D. Anderson, Protocol: Colorectal Cancer.
February 26, 1993	Theradex submits Protocol Amendment: Cervical/Colorectal Cancer Phase II, Summary of IND Submission.
March 5, 1993	Theradex submits Protocol: Cervical Cancer, Loyola Univ., Labels and certificates of analysis, Revised general investigational plan.
March 9, 1993	Theradex submits Request for Compassionate Use.
March 17, 1993	Theradex submits CMC update (Type I, Osaka plant).
March 23, 1993	Theradex submits authorization for the FDA to release Theradex's name.
March 24, 1993	Theradex submits Request for Compassionate Use.
March 26, 1993	Theradex submits Request for Compassionate Use.

DATE	EVENT
April 2, 1993	Theradex submits Request for Compassionate Use.
April 8, 1993	Theradex submits Request for Compassionate Use.
April 23, 1993	Theradex submits Request for Compassionate Use.
April 29, 1993	Theradex submits Protocol: Colorectal Cancer, Mayo Clinic.
May 6, 1993	Theradex submits Request for Compassionate Use.
May 14, 1993	Theradex submits IND Safety Report on the death of pt 19 at San Antonio.
June 3, 1993	Theradex submits Request for Compassionate Use.
June 23, 1993	Theradex submits Reply to FDA Comments.
August 4, 1993	Theradex submits Request for Compassionate Use.
August 4, 1993	Theradex submits Change in Protocol (MD Andersin/Amendment 5, CTRC/Amendment 3).
August 26, 1993	Theradex submits Request for Compassionate Use.
September 21, 1993	Theradex submits Request for Compassionate Use.
October 29, 1993	Theradex submits Annual Report.
November 9, 1993	Theradex submits Change in Protocol (Mayo Clinic/Amendment 3)
November 18, 1993	Amendment No. 040, The Upjohn Company submits transfer of sponsorship along with all rights and obligations to the application from Yakult Honsha Co., Ltd., to The Upjohn Company, Kalamazoo, MI.
November 30, 1993	Amendment No. 043 - Protocol Amendment.

DATE	EVENT
December 14, 1993	Letter from Division of Oncology and Pulmonary Drug Products, FDA, transfer of IND 35,229 accepted.
January 6, 1994	Amendment No. 044 - Protocol Amendment - Compassionate Use Protocol.
February 18, 1994	Amendment No. 045 - Protocol Amendment - Special Exception Protocol.
March 2, 1994	Amendment No. 046 - Protocol Amendment.
March 25, 1994	Amendment No. 047 - New Protocol M/6475/0006.
March 31, 1994	Amendment No. 048 - New Investigator for Protocol M/6475/0006.
April 11, 1994	Amendment No. 049 - TUC requests meeting with FDA to discuss development plans
April 21, 1994	Amendment No. 050 - Teleconference (4/5/94) follow-up.
April 26, 1994	Amendment No. 051 - Special Exception Protocol CPT-11/39424.
May 3, 1994	Amendment No. 052 - Protocol Amendment.
May 18, 1994	Amendment No. 053 - Protocol Amendment.
May 20, 1994	Amendment No. 054 - Special Exception Protocol.
June 2, 1994	Amendment No. 055 - Protocol Amendment
June 2, 1994	Amendment No. 056 - Request meeting to discuss the potential for filing a NDA for the use of irinotecan to treat patients with colorectal carcinoma.
June 7, 1994	Amendment No. 057 - Protocol Amendment.
June 9, 1994	Amendment No. 058 - 10 day written report.
June 23, 1994	Amendment No. 059 - Special Exception Protocol.

DATE	EVENT
June 23, 1994	Amendment No. 060 - Clinical Information - Follow-up to Amendment No. 058, 10 day written report.
July 5, 1994	Amendment No. 061 - The Upjohn Company added as a manufacturing site for the drug product.
July 14, 1994	Amendment No. 062 - Protocol Amendment.
July 21, 1994	Amendment No. 063 - Change in Protocol.
July 22, 1994	Amendment No. 064 - Requests telephone to discuss proposed toxicity program.
July 26, 1994	Amendment No. 065 - Additional documents for the August 3 meeting with FDA.
August 1, 1994	Amendment No. 066 - Item 7. Chemistry, B. Drug Product.
August 3, 1994	Meeting with Division of Oncology and Pulmonary Drug Products to review clinical development plan leading to NDA submission. Minutes of the meeting submitted to IND in Amendment No. 071, October 7, 1994.
August 11, 1994	Amendment No. 067 - 10 day Safety Report.
August 18, 1994	Amendment No. 068 - Information Amendment.
August 22, 1994	Amendment No. 069 - Information Amendment.
September 12, 1994	Amendment No. 070 - Protocol Amendment.
October 7, 1994	Amendment No. 071 - Information Amendment and minutes of 8/3/94 FDA meeting.
October 10, 1994	Amendment No. 072 - Annual Report No. 4.
October 18, 1994	Amendment No. 073 - Protocol Amendment.
October 26, 1994	Amendment No. 074 - Protocol Amendment.

DATE	EVENT
November 11, 1994	Amendment No. 075 - Information Amendment.
November 17, 1994	Amendment No. 076 - Protocol Amendment.
November 28, 1994	Amendment No. 077 - 10 day Written Safety Report.
December 1, 1994	Amendment No. 078 - Information Amendment.
December 2, 1994	Amendment No. 079 - Proposed trademark submitted: CAMPTOSAR® Sterile Solution (irinotecan hydrochloride sterile solution).
December 5, 1994	Amendment No. 080 - Information Amendment.
December 19, 1994	Amendment No. 081 - Submission of Clinical Benefit Report in response to commitment made at August 3, 1994 FDA meeting.
December 22, 1994	Amendment No. 082 - Protocol Amendment.
January 9, 1995	Amendment No. 083 - Protocol Amendment.
January 11, 1995	Letter to James Hamilton, Office of Compliance, FDA, requesting approval to defective clinical supplies.
January 27, 1995	Amendment No. 084 - Protocol Amendment.
January 30, 1995	Facsimile sent from Upjohn to Medical Reviewer with proposal for provision of case report forms (CRFs) for foreign studies to be included in the NDA. Several interchanges between sponsor and FDA.
February 13, 1995	Telephone call from CSO relaying the following resolution on foreign CRFs to be included in the NDA: "The sponsor does not need to include CRFs from foreign phase I studies in the NDA. However, the sponsor should be prepared to submit CRFs for patients who died and

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	experienced serious adverse medical events in phase II colorectal studies conducted in France and Japan."
February 16, 1995	Amendment No. 085 - Protocol Amendment.
February 20, 1995	Amendment No. 086 - Protocol Amendment.
February 22, 1995	Amendment No. 087 - Information Amendment, Additional Data for 3/10/95 FDA meeting.
February 28, 1995	Amendment No. 088 - Protocol Amendment.
March 6, 1995	Amendment No. 089 - Information Amendment: Aseptic Processing.
March 10, 1995	Meeting with Division of Oncology and Pulmonary Drug Products to review clinical benefit data; review of U.S. clinical trial experience (tumor responses, toxicity, and management of late diarrhea); filing proposal for treatment of previously treated colorectal cancer. Minutes of the meeting submitted to IND in Amendment No. 093, April 14, 1995.
March 14, 1995	Amendment No. 090 - Protocol Amendment.
March 14, 1995	Amendment No. 091 - Protocol Amendment.
April 4, 1995	Amendment No. 092 - Protocol Amendment.
April 14, 1995	Amendment No. 093 - Protocol Amendment.
April 26, 1995	Amendment No. 094 - Protocol Amendment.
May 16, 1995	Amendment No. 095 - General correspondence.
May 18, 1995	Amendment No. 096 - Protocol Amendment.
May 22, 1995	Amendment No. 097 - IND Safety Report - 10-day Written Report.

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May 25, 1995	Amendment No. 098 - General correspondence: Request for pre-NDA meeting.
June 6, 1995	Amendment No. 099 - General correspondence: Additional copies of Pre-NDA Meeting Request Package.
June 12, 1995	Amendment No. 100 - General Correspondence: Draft Protocol for Review.
June 16, 1995	Amendment No. 101 - Protocol Amendment.
June 19, 1995	Amendment No. 102 - Information Amendment.
July 6, 1995	Amendment No. 103 - General Correspondence: Response to FDA Request for Information (comments on proposed analysis plan).
July 20, 1995	Amendment No. 104 - General Correspondence: Request for C,M&C pre-NDA Meeting.
July 25, 1995	Amendment No. 105 - Protocol Amendment.
August 4, 1995	Amendment No. 106 - Safety Report: Follow-up Written Report.
August 7, 1995	Amendment No. 107 - General correspondence: Reply to Comments on Draft Protocol.
August 10, 1995	Amendment No. 108 - General correspondence: Package for CANDA/Protocol 0038 Statistical Plan Mtg.
August 11, 1995	Amendment No. 109 - New Protocol.
August 16, 1995	Correspondence: Desk copy of Protocols for Medical Officer.
August 28, 1995	Amendment No. 110 - Information Amendment.
August 28, 1995	Amendment No. 111 - Protocol Amendment.

DATE	EVENT
August 29, 1995	CANDA meeting.
September 5, 1995	Amendment No. 112 - Addendum to Request for pre-NDA Meeting; Revised Agenda.
September 13, 1995	Amendment No. 113 - Overheads for pre-NDA Meeting.
September 15, 1995	Amendment No. 114 - General correspondence: Response to FDA Request for Information - Clinical.
September 18, 1995	Amendment No. 115 - IND Safety Report: 10-day Written Report.
September 29, 1995	Amendment No. 116 - General Correspondence: CM&C Information - Teleconference report.
October 2, 1995	Amendment No. 117 - General Correspondence: Minutes of August 29, 1995 CANDA meeting.
October 4, 1995	Amendment No. 118 - Protocol Amendment.
October 4, 1995	Pre-NDA Meeting (all items except CM&C). The proposal to submit the FDA under the accelerated approval regulations (21 CFR § 314.510, Subpart H) was accepted. Design of the confirmatory phase IV trial was tentatively agreed upon; design to be finalized and submitted by early 1996.
October 11, 1995	Amendment No. 119 - General correspondence: Minutes of 9/6/95 CMC Pre-NDA Meeting.
October 23, 1995	Amendment No. 120 - Protocol Amendment.
October 30, 1995	Amendment No. 121 - Annual Report.
November 6, 1995	Amendment No. 122 - General Correspondence - Minutes of October 4, 1995, Pre-NDA Meeting.
November 8, 1995	Amendment No. 123 - Safety Report.
November 10, 1995	Amendment No. 124 - New Investigators.

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November 21, 1995	Amendment No. 125 - Protocol Amendment.
November 29, 1995	Amendment No. 126 - Safety Report.
December 1, 1995	Amendment No. 127 - Safety Report.
December 8, 1995	Amendment No. 128 - Safety Report.
December 13, 1995	Amendment No. 129 - Change in Protocol.
December 14, 1995	Amendment No. 130 - General Correspondence.
December 12, 1995	Amendment No. 131 - New Protocol.
December 28, 1995	NDA filed with and logged in to FDA.
December 28, 1995	Letter sent to Division of Information Systems Design (HFD-70) with listing of CANDA equipment.
January 3, 1996	Letter sent to Division of Information Systems Design (HFD-70) updating listing of CANDA equipment with information regarding the laptop computers for the medical reviewers.
January 11, 1996	Leslie Vaccari (CSO) called and requested immediate installation of the CANDA hardware (scheduled installation of 1/8/96 cancelled by FDA closure from 1/8 through 1/10 due to weather). CANDA equipment delivered same day by A.A. Khan and J.P. Maile. SAS data sets were hand delivered by R.E. Gibson.
January 11, 1996	Leslie Vaccari informed MAB that page 5/1/32 was missing from the reviewer copy. Replacement page was faxed.
January 16, 1996	Fax from Leslie Vaccari thanking P&U for 1/11/96 CANDA installation.
January 16, 1996	Fax from H.J. DeKoning Gans to FDA. Requested feedback on proposed cut off date (12/31/95) and content of NDA Safety Update.

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January 17, 1996	Telephone request from Leslie Vaccari to D.C. Beuving. Requested: immediate CANDA training for medical reviewers; location of specific data within NDA; investigator information on behalf of FDA Division of Scientific Investigations.
January 18, 1996	FDA fax responding to P&U fax of 1/16/96. FDA requests that the safety information provided be consistent with the ISS content submitted in NDA 20-571.
January 18, 1996	A.M. Holt and A.A. Khan provide CANDA training to FDA medical reviewers, Drs. Murgo and Chico. A.M. Holt delivered investigator information requested during 1/17/96 telephone conversation between D.C. Beuving and Leslie Vaccari. Medical reviewers forwarded request for information (summarized in contact report from A.M. Holt dated 1/22/96).
January 19, 1996	Fax from D.C. Beuving to Leslie Vaccari. Provided response to location of patient data requested by Dr. Murgo during 1/17/96 telephone conversation between D.C. Beuving and Leslie Vacari.
January 22, 1996	FDA acknowledgement letter for the NDA (dated 1/22/96). Confirms date of FDA receipt of the application as 12/28/95. Indicates that unless notified to the contrary, the application will be filed in 60 days (calculated as 2/27/96).
January 22, 1996	Dr. Turner (Scientific Investigations) called M.A. Baumgartner to request investigator information and protocol information from pivotal trials.
January 23, 1996	Replacement battery for Dr. Murgo's laptop shipped via overnight mail.
January 25, 1996	Leslie Vaccari called M.A. Baumgartner to request information regarding addresses and DMFs for the Japanese manufacturer and subcontractors for the drug substance. This information is needed to

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	support scheduling of the PAI. During the conversation Leslie Vaccari reported that the replacement battery mailed 1/23 is also defective after charging. She requested a second battery.
January 26, 1996	Fax from M.A. Baumgartner to Leslie Vaccari provides requested facility addresses for Yukult Honsha, Sato and Shiratori. Also, addressed DMF issue and provided primary contact at Yukult for DMF 8553.
January 26, 1996	Second replacement battery mailed to Leslie Vaccari for 1/29/96 delivery.
January 29, 1996	Leslie Vaccari called to say that, regarding the EA, it may delete certain format items under the recent guidance to industry (announced in 1/11/96 FR). She suggested that "withdrawal" can be accomplished by superseding via submission of modified EA through the Amendment mechanism.
January 29, 1996	Fax received on EA issue.
January 30, 1996	Submitted response to reviewer questions on the CANDA (from A.M. Holt at the 1/18/96 training session). Submitted as Amendment 001 to the NDA.
January 31, 1996	Submitted response to Dr. Turner's request for protocols, CI information and volume 1.1.
February 1, 1996	Dr. Turner called and identified the CIs to be audited; to request specific CRFs and ADR listings for the CIs identified.
February 6, 1996	Submitted response to Dr. Turner's 2/1/96 request.

DATE	EVENT
February 12, 1996	Telephone contact with Leslie Vaccari. 45 day meeting will be held today. The review team is planning on a June ODAC with an action letter shortly thereafter. Would like revised EA submitted ASAP (prior to 60-day milestone).
February 13, 1996	Telephone contact with Leslie Vaccari. No major deficiencies noted at the 45-day meeting. Planning on a June ODAC. Action letter could come as early as 6/28/96.
February 13, 1996	Dr. Chico contacted A.A. Khan to resolve some CANDA export problems. A telephone conference will be needed to resolve. Message left on Chico's voice mail suggesting call on February 14, 1996.
February 14, 1996	Mailed Amendment 002 to the NDA which contained the revised EA and two corrected pages for Item 3. Corrected CMC pages sent to Detroit office for inclusion in field copy.
February 14, 1996	Contacted Leslie Vaccari to facilitate scheduling a teleconference with Dr. Chico.
February 16, 1996	Fax from Leslie Vaccari to MAB. Comments from Biopharm reviewer. Request for PK data availability in an electronic format.
February 20, 1996	Telephone call with Leslie Vaccari regarding the desire of the biopharm reviewer to get the electronic information detailed in the fax of 2/16. Annette Holt spoke with Dr. Chico regarding the database issues. MAB followed up and offered assistance with respect to producing custom datasets.

DATE	EVENT
February 21, 1996	Larry Schaaf (Clin. PK) spoke with Dr. Williams. It was agreed to send WP 5.2 files immediately for the Item 6 summary and to provide data sets for the "pivotal" phase II studies. Larry Schaaf to call Dr. Williams with estimates of time frame for data sets for Phase II and with results of assessment of feasibility for data builds for the Phase 1 studies conducted by Yakult/ Daiichi/Besselar.
February 22, 1996	MAB spoke with Leslie Vaccari regarding submission of disks. She requested two sets of disks be formally submitted to the application as general correspondence (PK and archival jackets). This and all future letters should be submitted in NDA jackets to expedite processing in the document control room. Letter/disks sent by overnight mail.
February 22, 1996	M.A. Clasby met with FDA inspector Tom Hillary regarding other issues. During the conversation the issue of the CPT-11 PAI was raised. He has tentatively agreed to conduct the PAI starting April 15.
February 23, 1996	A telecon was held between Schaaf, Baumartner and P&U consultants Grasela and Fieldler-Kelly. Reached agreement on additional deliverables.
February 27, 1996	Faxed summary of 2/23/97 teleconference to FDA Project Manager, Leslie Vaccari.
February 28, 1996	Data sets used for structural models plus control streams provided to Dr. Williams by Fiedler-Kelly.
March 1, 1996	Remainder of Phase II data sets sent to Williams by Fieldler-Kelly.
March 7, 1996	Data sets for Phase I studies 0027 and DM111 sent to Williams.

DATE	EVENT
March 7, 1996	Telephone conversation between Dr. Williams and Larry Schaaf. Updated Dr. Williams regarding status of response.
March 8, 1996	Telephone conversation between MAB and Leslie Vaccari. Review continues to proceed smoothly. Modified EA was hand delivered to HFD-357 (Nancy Sager's group). The Microbiology review is back; no deficiencies noted. Trademark review will occur at the end of this month. Leslie OK'd upgrade of the export software for the CANDA. A. Khan will install 3/11/96.
March 8, 1996	From M.A. Clasby from interaction with inspector Tim Hillary: the CPT-11 pre-approval inspection in Kalamazoo is now scheduled to start on Wednesday, April 17th rather than Monday, April 15th. The change has been made so that the PAI for Remifentanil can occur on the 15th and 16th of April.
March 22, 1996	General Correspondence - NDA Safety Update.
April 3, 1996	Amendment 004 - Response to Request for Information - Additional use report forms.
April 4, 1996	Desk copies of updated SAS Datasets (safety and efficacy) sent to Leslie Vaccari. It was agreed with Leslie that Archive copy would follow.
April 5, 1996	PAI scheduled for Kalamazoo changed to begin 4/29/96-4/30/95 per contact between Martha Clasby and Tim Hillary.
April 15, 1996	Amendment 005 - Updated Summary of Efficacy.
April 18, 1996	PAI finished at Sato with 483 issued with 2 minor observations. Approval will be recommended. Shiratori will be inspected the 19th with Yakult finished up by the 26th.

DATE	EVENT
April 18, 1996	The PAI scheduled for 29th and 30th in Kalamazoo will need to be rescheduled at FDA's request (schedule conflict with FDA Inspector, Tim Hillary) for May 7.
May 8, 1996	General Correspondence - Response to Information Request.
May 16, 1996	Amendment 006 - Response to FDA Request for Information - Environmental Assessment.
May 16, 1996	Oncologic Drugs Advisory Committee Brochure - for June 13, 1996 meeting.
May 16, 1996	Sent to desk copies of Oncologic Division Advisory Committee Brochure and copy of revised Environmental Assessment to Ms. Leslie Vaccari as requested during 5/16/96 telephone conversation.
May 16, 1996	Correction to Oncologic Drugs Advisory Committee Brochure. Correction of Protocol.
May 21, 1996	Response to telephone facsimile transmission of May 17, 1996 requesting additional information regarding stability data.
May 21, 1996	General correspondence - response to request for information.
May 28, 1996	Amendment 007 - Correction to Clinical/Statistical Information (Amendment 003). Page 57 of Volume 1, section 8, "Discontinuations Due to Death and/or On-Study Deaths".
May 29, 1996	Amendment 008 - Chemistry, Manufacturing, and Control section - labeling. Copies of proofs for vials, cartons, and blister packs for the product.
May 29, 1996	Desk Copies of Amendment 008 providing proofs of labels for vials, cartons and blister packs. Sample of blister pack with an empty, uncapped vial enclosed.

DATE	EVENT
May 30, 1996	Amendment 009 - Phase 4 Study - Prot. M/6475/0038 mentioned in letter.
May 31, 1996	Correction to Oncologic Drugs Advisory Committee Brochure. Previous package erroneously included the outdated statistical section.
June 4, 1996	Amendment 010 - Response to FDA Request for Information - Environmental Assessment - Revised EA information: Format items 9 and 10.
June 5, 1996	Received missing pages from the background material submitted by the Oncology Division. Also included was a draft of the questions prepared by the division for TUC.
June 6, 1996	General Correspondence - Response to FDA Request for Information - Postmarketing Study Commitments. Prot. M/6475/0038, M/6475/0037, M/6475/0033, M/6475/0062 mentioned in response letter.
June 6, 1996	General correspondence - Response to FDA Request for Information (May 31, 1996 facsimile request) - Microbiologist's Request for Postmarketing Commitments.
June 7, 1996	Amendment 011 - Response to FDA Request for Information. (Per fax of 6/4/96).
June 7, 1996	Oncologic Drugs Advisory Committee (ODAC) - Providing a list of consultants who will be at the 6/13/96 ODAC Meeting as requested by FDA.
June 10, 1996	Amendment 012 - Response to FDA Request for information related to chemistry review.
June 10, 1996	General Correspondence - Request for Teleconference. Letter to Dr. Delap re questions which will be presented at the ODAC.

DATE	EVENT
June 11, 1996	Amendment 013 - Response to FDA Requested Changes to the Product Labeling. In response to FDA's 5/31, 6/3, 6/7 and 6/10 facsimiles.
June 11, 1996	Proposed news release pending a favorable recommendation at the Oncologic Drugs Advisory Committee Meeting. Also attached is the current draft package insert.
June 12, 1996	Letter to Tracy Acker requesting comments of proposed news release with background information pending favorable recommendation for approval by the ODAC.
June 12, 1996	MACMIS ID #4364 - Letter to K.J. Day providing comments regarding proposed press release in the event of a favorable recommendation for approval by the ODAC.
June 13, 1996	MACMIS ID #4364 - Response to proposed press release following the ODAC meeting on 6/13/96.
June 14, 1996	FDA letter giving approval of NDA 20-571 providing for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed following 5-FU-based therapy.
June 14, 1996	General Correspondence - Response to FDA Request.